

CCT CORE TREAT Fracture Study: Time savings by Rapid EMS Antibiotic Therapy for Fractures

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Summary

Increasing emphasis is being placed on air medical research studies demonstrating both outcomes improvement and cost-effectiveness. One area of potential benefit is air transport crew administration of intravenous antimicrobial therapy (IVAT) to trauma scene patients with open fractures. Preliminary work from the Critical Care Transport Collaborative Outcomes Research Effort (CCT CORE) study group has identified often-prolonged time intervals between air medical crew patient encounter and ultimate antibiotics administration at receiving trauma centers. This study, the *Time Savings by Rapid EMS Antibiotic Therapy for Fractures* (TREAT Fx) project, has three major aims. First, TREAT Fx aims to fully characterize potential time savings accrued by air medical crew antibiotics administration. Second, TREAT Fx aims to ascertain whether earlier IVAT reduces open fracture complication rates. Third, the study will assess costs associated with open fracture complications, facilitating calculation of cost-effectiveness of air medical crew IVAT.

Abbreviations

CCT CORE	Critical Care Transport Collaborative Outcomes Research Effort
ED	Emergency Department
EMS	Emergency Medical Services
FARE	Foundation for Air-Medical Research and Education
GCS	Glasgow Coma Scale (score)
HEMS	helicopter emergency medical services
HEMS abx	study group of scene trauma patients who receive IVAT from HEMS crews
Hosp abx	study group of scene trauma patients who receive IVAT from receiving hospitals
IRB	Institutional Review Board (research ethics review panel)
ISS	Injury Severity Score
IVAT	intravenous antibiotic therapy
TREAT Fx	Time Savings by Rapid EMS Antibiotic Therapy for Fractures study

Introduction

This document outlines the Time Savings by Rapid EMS Antibiotic Therapy for Fractures (TREAT Fx) study. TREAT Fx will continue a preliminary hypothesis-generating project that was executed as part of a FARE-supported CCT CORE study. In the initial work, it was found that there was a potential for substantial time savings associated with HEMS crew administration of IVAT to open fracture patients at trauma scenes. TREAT Fx aims to extend the results of the pilot study, assessing time savings, clinical endpoints, and cost-effectiveness of HEMS IVAT for open fractures.

The TREAT Fx study group comprises a number of CCT CORE-participating HEMS programs. The number of participating programs is important for at least two reasons. First, the study *n* will be enhanced by the multicenter nature of the project. More importantly, the study will take advantage of existing heterogeneity in HEMS program practices that create a “natural experiment.” The specific heterogeneity of interest is the lack of uniform practice with respect to scene administration of IVAT for trauma patients with open fractures.

Most HEMS programs’ protocols (and formularies) do not allow for prehospital IVAT. However, some HEMS programs do carry (and administer) IVAT for patients with suspected open fractures. Thus, neither medical protocol changes nor subject randomization are required to assess the impact of HEMS IVAT on timing, clinical, and cost-effectiveness endpoints. (Independent and unrelated to their participation in TREAT Fx, some participating HEMS programs are considering changing protocols to allow for HEMS IVAT. For these programs, TREAT Fx analysis will incorporate a “before-and-after” approach.) The differing, and evolving, practices with respect to participating programs allow for a study which is observational in nature, but which should yield results of substantial clinical and economic impact.

The clinical importance of TREAT Fx stems from the desirability of early IVAT for open fractures. While a cutoff time for institution of IVAT is not precisely characterized, it is known that early IVAT plays an important role in optimizing outcomes from open fractures.¹ The TREAT Fx study premises are:

- 1) Early IV abx therapy of open fractures is an important determinant of limb outcome.
- 2) The relatively high acuity of air transported trauma patients means that HEMS crews often encounter trauma scene patients with open fractures.
- 3) Scene characteristics (*e.g.* entrapment) and logistics (*e.g.* transport time) often prolong the time interval between HEMS arrival at patients, and ultimate patient arrival at the receiving trauma center. (Furthermore, even when patients get to receiving trauma centers quickly, there may occasionally be delays to IVAT.)
- 4) HEMS crew administration of IVAT to patients with open fractures is thus likely to be associated with a significant reduction in “time-to-IVAT,” accruing substantial benefit with little risk.
- 5) The cost-effectiveness of HEMS IVAT is likely to be favorable, given the very low costs (or risks) associated with HEMS IVAT. Furthermore, since ground EMS agencies do not now (and are not likely to soon) carry antimicrobials, any benefits associated with HEMS IVAT can be used as a cost justification for air medical transport. This is important, given the high costs of additional hospitalization time (including repeat operative intervention) associated with infected open fractures.

The current evolution of HEMS prehospital IVAT protocols (*i.e.* the fact that some programs give IVAT, some don’t, and some are in the process of implementing them) sets up a natural experiment.

The surrogate endpoint of time-to-IVAT, and the clinical endpoints as well, can be assessed in scene-transported HEMS patients who do, as compared to those who do not, receive prehospital IVAT. This analysis can be executed across multiple HEMS programs, and for some programs (whose IVAT protocols are evolving independent of TREAT Fx) a before-and-after analysis will be enabled. TREAT Fx does not randomize any patients, but rather follows different clinical care patterns over time, both within and across HEMS programs. Thus, the study can address important questions about this clinical intervention without interfering with, or dictating, clinical care for the patients who will comprise the study population.

Background & Study Justification

A. HEMS and trauma outcomes improvement: The case for assessing a new class of endpoint

It is well known that HEMS is associated with improvement in trauma mortality. While there is ongoing and appropriate debate about triage and utilization review, the preponderance of the available evidence makes an extremely strong case for mortality reduction with HEMS scene and interfacility transport.²⁻⁴

The evidence is less clear about specific reasons for outcomes improvement associated with HEMS. There is evidence that air-transported trauma patients' major morbidity and mortality are positively influenced by both basic (e.g. intravenous access) and advanced interventions (e.g. airway management).⁵⁻⁸ In terms of other trauma endpoints, there is a paucity of data. Furthermore, the data that have been reported often address "soft" endpoints (e.g. improved pain management)⁹⁻¹³ that, while important, are difficult to quantify and thus not easily translated into cost-effectiveness and HEMS justification analyses.

Without disputing the importance of endpoints assessed in existing studies, the TREAT Fx study group believes other outcomes also warrant attention. In an arena of appropriate scrutiny of HEMS costs and appropriate utilization, equally rigorous scrutiny should be directed towards previously uncharacterized benefits that may contribute to HEMS cost justification. The TREAT Fx study is, in short, directed at assessing the previously uncharacterized potential benefit of early IVAT for scene trauma patients with open fractures.

B. Medical justification for studying open fractures

Why assess open fractures? There are certainly a number of HEMS-related diagnoses and interventions, even within the category of scene trauma, that pique interest and prompt debate. The open fracture subgroup of trauma patients was selected for study by the TREAT Fx group because 1) these patients have a discrete injury relatively easily identified in the field, 2) patients with open fractures are encountered often by HEMS units, and 3) the straightforward and easily implementable intervention of interest (IVAT) is already provided by some – but not all – HEMS programs. This last fact is critical, as it allows for an observational natural experiment study design.

Early IVAT for open fractures, in order to treat inevitable contamination, has been identified as a major contributor to optimal outcome since the 1970s.^{1, 14} As an American Academy of Orthopedic Surgeons Instructional Course Lecture notes, "To prevent a clinical infection, immediate antibiotic administration" is necessary.¹ The same source, indicating that antibiotics "should be given as soon as possible," points out that time to antibiotic therapy – but not duration of IVAT or timing or type of wound

closure – is a “significant variable” in determining open fracture outcome.^{1, 15, 16} Cochrane review confirms the utility of early antibiotic therapy for treatment of open fractures.¹⁷ Other authoritative sources agree that “available evidence suggests that antibiotic treatment should be initiated as soon as possible following injury.”¹⁸

Existing data clearly show that delay of IVAT by 3 or more hours worsens outcome.¹⁵ However, there is little or no reason to assume that the 180-minute time is a dichotomous cutoff. It is simply the time frame that’s been studied in the past. In fact, what limited (experimental animal) data there are, show that the earliest possible IVAT – pretreatment – is associated with the lowest risk of infectious complication.¹⁹

The widespread acknowledgment of the time-criticality of IVAT, and the lack of any data addressing differing time frames of IVAT administration within the accepted 3-hour window, render it reasonable to ask the question: Can prehospital institution of IVAT improve outcome? There is little if any reason to believe early IVAT to be associated with significant risk, and it is quite plausible that benefit can be accrued by rapid IVAT. As precedent, there are many examples of diagnoses (*e.g.* stroke, cardiac) in which initial dichotomous cutoff times for intervention windows (for lysis or cath lab intervention) have evolved with demonstration of more linear associations between rapidity of therapy and beneficial outcome.^{20, 21} In short, TREAT Fx is based upon the physiologically sound principle, that earlier IVAT for open fractures is associated with little or no risk, and that such early therapy is likely to benefit some patients.

C. Research methodology justification for assessing open fractures

Open fracture is but one of many diagnoses that would be productive areas for HEMS research focus. However, there are some characteristics about open fracture treatment that render this diagnosis particularly well-suited to a trial assessing logistic, clinical and cost outcomes. This section outlines the endpoints to be addressed, and explains why these endpoints should be relatively easy to study.

With respect to logistic (time savings) outcomes, the assessment of open fracture outcomes is simple. Assessment of time savings associated with prehospital administration of IVAT will be facilitated by the nature of the intervention (IVAT administration) and the reliability of HEMS prehospital times and (where applicable) IVAT administration times by HEMS and receiving hospitals. The intervention in question, administration of a drug, is highly amenable to analysis by chart review, given the common systems for documentation of administered drugs. Previous HEMS studies have easily obtained the timing information of drugs administration in the field and in the ED, and have also used the TREAT Fx methodology of assessing time savings accrued by HEMS therapeutic intervention.^{11, 12, 22}

Fracture site clinical outcomes can also be easily dichotomized, using chart review of unbiased diagnostic information. The major clinical endpoints of TREAT Fx are 1) infection at the fracture site (yes or no), 2) non-union at the fracture site (yes or no), and 3) infection/non-union composite endpoint (yes if either, no if neither). The focus of the study on fracture site complications, with appropriate adjustment for level of injury (*e.g.* with Injury Severity Score) and comorbidity presence, will allow for accurate assessment of a discrete set of clinical endpoints of high relevance and impact.

With respect to cost-related outcomes, TREAT Fx will assess endpoints related to interventions and hospitalization related to any complications that occur. Again, the discrete nature of orthopedic trauma-associated costs will aid in ascertainment of cost-related endpoints. For TREAT Fx, major cost

outcomes will include 1) need for reoperation, 2) fracture-specific hospital costs such as prolonged length-of-stay and/or antibiotic cost. To the extent that it is possible, TREAT Fx will also assess other endpoints such as additional rehabilitation (and out-of-work time) associated with occurrence of infection and/or non-union.

Open fractures are thus an excellent, discrete clinical subject for HEMS research. The assessment of logistics/timing and clinical endpoints can be easily performed in an unbiased manner. Some treating orthopedists may be aware that their patients have received IVAT by HEMS, but there is no concern for bias in the assignment of diagnoses of infection or non-union. The clinical suitability for open fracture research extends to cost-effectiveness analysis. The investigators believe the focus of a HEMS study on open fracture treatment represents an important chance for air transport providers to demonstrate morbidity-related cost-effectiveness for scene trauma. The TREAT Fx study group has confidence that the study will find that the cost savings associated with preventing even a few open fracture complications, will outweigh the costs of providing HEMS service for a much larger group of trauma patients.

D. Open fracture medical considerations and management

This section's part 1 outlines fracture classifications, and provides an overview of the risks of fracture complications associated with different types of open fractures. Part 2 addresses varying regimens for open fracture antibiotic therapy.

1) Open fracture classification and infection risks

A classification system (Gustilo and Anderson, subsequently modified by Gustilo *et al*)²³ is the most widely used method for grouping open fractures.¹ In this system, a Type I open fracture indicates a puncture wound of 1cm or less with minimal contamination or muscle crush. Type II open fractures consist of a laceration of more than 1cm in length, with moderate soft-tissue damage and crushing; bone coverage is adequate and comminution is minimal. Type III open fractures involve extensive soft-tissue damage and significantly contaminated wounds (Type IIIa) with bone exposure (Type IIIb) and/or arterial injury (Type IIIc).¹ Unfortunately, due to poor inter-rater reliability – even when orthopedic surgeons are questioned – authoritative sources recommend that classification of the open fracture should only be done in the operating room, after wound exploration and debridement.

Reviews place the risk of clinical infection of open fractures as 0-2% for Type I, 2-10% for Type II, and up to 50% for Type III (5-10% for IIIa, 10-50% for IIIb, 25-50% for IIIc).¹ A representative landmark study from 1989 provides specific infection rates of 1.4% for Type I, 3.6% for Type II, and 22.7% for Type III.¹⁵ Other factors known to adversely impact the likelihood of development of complications from open fractures include tibial involvement and presence of diabetes, collagen vascular disease, chronic venous insufficiency, immunocompromise, and previous fractures or surgical incisions over the involved area.^{1, 15, 24}

One widely referenced system for assessing open fracture infection propensity assigns risk based upon the number of medical and immunocompromising factors.¹⁸ Variables assessed included age>79, smoking, diabetes, malignancy, pulmonary insufficiency, and systemic immunocompromise. Infection rates were 4% for patients with none of the preceding variables;

infections occurred at rates of 15% in patients with 1 or 2 of the preceding variables, and in 31% of patients with more than 2 of the risk factors.²⁵

2) Antibiotic therapy for open fractures

The exact nature of the IVAT for open fracture therapy is subject to ongoing debate, with reviews noting that “while there is ample data supporting the administration of antibiotics after open fracture, evidence indicating an optimal regimen is lacking.”¹⁸ Authoritative sources point out that while both gram-positive and gram-negative coverage is necessary, the systemic administration of agents with gram-negative activity may be unnecessary if aminoglycoside-impregnated beads are used for local antibiotic delivery.^{1, 26} Thus, a variety of approaches for immediate (prehospital) IVAT – ranging from single-agent therapy with a first- or third-generation cephalosporin to addition of an aminoglycoside to gram-positive agents – are justifiable as consistent with available expert recommendations.

The acceptability of multiple approaches for IVAT is an important contributor to the ethics of the non-interventional design of TREAT Fx. Neither the decision to administer IVAT in the prehospital setting, nor the selection of a particular IVAT approach, is dictated by the current standard of care. Thus, the investigators judge ethical an observational study that assesses approaches ranging from no IVAT, to therapy with varying agents.

E. Natural experiment design for assessing open fracture treatment: Now is the time

The ability to execute a natural experiment design is a critical advantage to selection of open fractures as a study diagnosis. This is in large part due to the understandably complex ethical issues surrounding acute care research. The concept of (non-physician) HEMS crews interrupting trauma scene care to obtain consent is, to say the least, problematic. Even in the Emergency Department (ED), just the community consultation and notification for trials on patients who can’t easily give consent can require many years and hundreds of thousands of dollars (personal communication, Dr. Jill Baren, co-PI of NIH Pediatric Seizure Study, 15 February 2007). For studies focusing on the prehospital setting, randomized controlled trials are few, and may engender resource requirements that are nearly prohibitive. One of the only (if not *the* only) true randomized controlled trials in HEMS, the Head Injury Retrieval Trial (HIRT), is led by a TREAT Fx co-investigator who estimates HIRT’s time and funding requirements at over 6 years and \$8 million (personal communication, Dr. Alan Garner, 22 October 2008). Thus, the ability to assess a clinically important outcome with an observational design is a prime advantage of TREAT Fx.

The natural experiment design has been used to good effect in previous HEMS studies. Some investigators have assessed the mortality impact of gain (or loss) of air medical resources.²⁷⁻²⁹ Other investigators have reported on natural experiments involving temporary HEMS availability issues (*e.g.* due to weather or maintenance).^{30, 31} Thus, there is precedent for use of the natural experiment approach in prehospital and HEMS research.

While even the best natural experiment design is not as good as randomized control trial, there are specific circumstances rendering 2009 an ideal time for a natural experiment approach to assessing prehospital open fracture IVAT. Most importantly, HEMS programs have the option of providing IVAT for open fractures, or not providing such therapy. TREAT Fx investigators do not claim HEMS IVAT for open fractures to be the standard of care, and this view justifies an observational study. In 2009, some

HEMS programs (independently of the TREAT Fx study) are moving towards changing prehospital protocols to allow for HEMS IVAT. Thus, the power of assessing HEMS IVAT and associated endpoints across many HEMS programs with varying IVAT practice, will be enhanced by subgroup analyses of same-program endpoints, “before-and-after” institution of IVAT. The TREAT Fx investigators thus believe that not only is assessment of IVAT for open fractures an excellent subject for a HEMS study, but that the changing standards and care practices render 2009 an ideal time for an observational study.

F. Summary of background and study justification

The focus of a major new HEMS study initiative on a previously underemphasized area has numerous benefits in extending knowledge of clinical and cost-effectiveness benefits of air medical scene response. Open fractures are particularly amenable to study due to a variety of factors, including the following:

- 1) HEMS crews encounter open fractures with high frequency. Thus, if early IVAT is clinically useful, HEMS will be improving clinical (and cost) outcomes in a very large group of patients.
- 2) Since IVAT is provided by very few (if any) ground EMS providers, any demonstrated benefit to IVAT will be clearly attached to air medical transport services.
- 3) The evolving standard of care with respect to HEMS IVAT is currently providing a valuable research window for observational study. Changing practices enable a non-interventional study to be characterized by methodological rigor approaching the gold-standard randomized controlled trial design.
- 4) The discrete nature of extremity trauma allows for unbiased assessment of clinical endpoints, as well as cost assessments specifically associated with development of open fracture complications.

Methods

A. Design

TREAT Fx is a non-interventional (observational) study of a consecutive series of cases transported by a number of participating HEMS services. The study’s design allows for comparison of endpoints across different HEMS programs that have differing practices with respect to prehospital IVAT. The design also allows for intra-program comparison, for those programs that change their practices; for these programs a “before-and-after” analysis will be used. For a pooled overall analysis, the study will group all subjects as to whether the transporting HEMS service provided IVAT.

B. Setting and participants

- 1) Study HEMS programs:

The study will occur in a variety of settings, to be determined by the HEMS program participants. At this time, the participants come from the following HEMS programs:

Air Care (Cincinnati)	Life Flight of Maine	Mayo One
Boston MedFlight	LifeNet of New York	Tulsa Life Flight
MedFlight of Ohio	StatAir (Texas A&M)	NRMA Care Flight (Australia)

The programs above comprise a broad range of HEMS service types and geographic and clinical areas. It is hoped that additional programs may join as the project continues, and the nature of TREAT Fx is such that programs can be added at essentially any time (since there is unlikely to be a difference/improvement in outcomes associated with open fractures with the passage of a few months' time after study commencement).

2) Study patients:

Study patients are those with HEMS-diagnosed open fractures. For HEMS programs that administer IVAT for scene trauma patients with open fractures, those programs' TREAT Fx patients will have received HEMS-administered IVAT. For those HEMS programs that do not carry antibiotics, the TREAT Fx patients will be those scene trauma patients in whom HEMS crews document high clinical suspicion of open fractures.

It is understood that the prehospital definition of patients as having open fractures is imperfect. Since misclassification is likely to be in the false-positive direction (*i.e.* "overcall" of open fractures), and this direction results in study bias toward the null, the TREAT Fx investigators do not believe the imperfect nature of prehospital open fracture diagnosis to be a significant problem.

C. Data collected

The study data to be collected consist of information about both times and clinical interventions in the prehospital and ED settings. Data on hospital course will be collected to reflect ultimate diagnosis and course, and to allow assessment of cost endpoints. Data will also be collected, to allow for description of the patient population, and to enable multivariate adjustment for variables known to be associated with the endpoints of interest. [For this section, "fx" refers to "open fracture(s)."]

1) Prehospital data points

a. Incident time and times of:

- | | |
|----------------|------------------|
| ○ HEMS arrival | ○ HEMS departure |
| ○ HEMS IVAT | ○ HEMS pass-off |

b. Patient descriptors:

- | | |
|---------------------|-----------------------------|
| ○ age, race, sex | ○ any hypotension |
| ○ intubation status | ○ open fx site(s) suspected |
| ○ GCS | ○ neurovascular exam |

2) ED data points

a. Time of IVAT if given in ED

b. Patient descriptors: ED diagnosis and modifiers of open fracture infection risk:

- | | |
|--------------------|-------------------------------------------------------------|
| ○ age >79 | ○ collagen vascular disease |
| ○ smoking | ○ chronic venous insufficiency |
| ○ diabetes | ○ pulmonary insufficiency |
| ○ malignancy | ○ previous fractures/surgical incisions at the open fx site |
| ○ immunocompromise | |

3) Hospital course data points

a. Times of IVAT (if first administered other than in ED) and initial debridement in OR

b. Patient descriptors

- ISS
- non-extremity trauma
- c. Interventions
 - OR day(s) for fx
 - hosp. days/disposition
- d. Outcomes (assessed/judged by orthopedists blinded to HEMS vs. non-HEMS IVAT)
 - non-union (6 mnths)
 - fx-associated costs
 - fx location(s)
 - type(s): I, II, IIIa, IIIb, IIIc
 - days of IV antibiotics
 - days wound left open
 - operation(s) for fx
 - infection (at 3 months)

For the assessment of infection, there will be subcategories for superficial infection and deep infection. The distinction will be important for cost considerations, since the former are treated with oral antibiotic therapy and the latter require reoperation (as well as 6 weeks of intravenous antibiotic therapy). The infection endpoint will be judged to have been met if orthopedic reviewers (blinded to HEMS Abx status) judge infection to have been present. Other factors assessed, such as time to initial debridement and number of days wound left open (with vacuum or sterile dressing), will be used primarily to adjust for potential confounding of an association between early IVAT and infection outcome.

D. Analysis plan and sample size/power calculations

The power and sample size endpoints are driven by the anticipated fracture complication rates, with infection being the endpoint driving sample size estimates. Sample size planning assumes that an n sufficient for assessment of the fracture complication endpoint, will be more than adequate for robust analysis of both time-to-IVAT and cost endpoints.

Analyses will focus on comparison between two groups, defined by whether the first dose of IVAT for open fracture was administered by HEMS crews or at receiving hospitals. Patients receiving HEMS IVAT will comprise the “HEMS Abx” group; patients who do not receive initial antibiotic therapy until arrival at the receiving hospital will constitute the “Hosp Abx” group. All statistical testing will be performed with STATA 10MP (StataCorp, College Station TX), and statistical significance will be defined at the $p < 0.05$ level.

1) Time to IVAT

- a. Like most time-to-event data, the time-to-IVAT endpoint is expected to be non-normally distributed. This non-normality of the data will be tested using the Shapiro-Wilk W test.
- b. Assuming times are found to be non-normally distributed, these data will be analyzed with nonparametric approaches. Ranges and interquartile ranges (IQR) will be used to depict spread of data. Central tendency will be reported as medians, with bootstrapped 95% confidence intervals (CIs) calculated after the method of Haukoos.³²
- c. Pilot study from 4 HEMS programs reveals that the median time savings potentially accrued with HEMS IVAT is of potential clinical significance. As noted above, the precise time frame constituting “early” IVAT is not known. Based upon literature review and trauma orthopedist expert opinion, the pilot study defined 30 minutes as an *a priori* cutoff for “potentially significant time savings.” The pilot study found

the median time between HEMS crew initial encounter with scene open fracture trauma patients, and subsequent HEMS crew pass-off of patient to receiving hospitals, was 33 minutes (IQR 24-42). In nearly 60% of cases overall (and in 72% of rural-based HEMS transports), the potential time savings for HEMS IVAT exceeded 30 minutes. Even for urban-based HEMS services, the median time savings potentially accrued by HEMS IVAT approached 30 minutes (median 28 minutes, IQR 24-40). For rural HEMS services, the time savings were greater (median 35 minutes, IQR 26-45).

- d. HEMS Abx vs. Hosp Abx patients' times to IVAT will be compared with Kruskal-Wallis testing.
 - e. Due to the large number of patients to be accrued (see discussion below), the TREAT Fx design will allow for precise estimates, and robust comparisons, for the Time-to-IVAT variable. Large numbers will also enable stratified analysis (*e.g.* time to IVAT in various age groups), which will be performed primarily for hypothesis-generating purposes.
- 2) Costs attributable to open fracture management
- a. Costs will be compared between the HEMS Abx group, and the Hosp Abx group, using nonparametric techniques.
 - b. Costs of HEMS transport and subsequent hospitalization costs attributable to open fracture care, will be analyzed descriptively. These data will be used for cost-effectiveness analysis.
 - c. If significant differences are found for fracture-site complications (see below), then number-needed-to-treat (*i.e.* number needed to transport) analysis will be performed to ascertain how many open fracture patients must be flown to prevent one case of open fracture complication. This information will be combined with the cost of HEMS transport, and the cost of open fracture complication, to enable cost-effectiveness calculation.
- 3) Fracture-site complications
- a. Two fracture-site clinical endpoints will be assessed: infection and non-union. Given its relative frequency, ease of adjudication on records review, and presence of reliable data outlining expected baseline occurrence rates, the infection endpoint is used as a basis for sample size and power calculations. (However, in the final analysis, overall complication rates will be compared for HEMS Abx vs. Hosp Abx cases, to assess for differences in the composite endpoint of infection or non-union.)
 - b. Two factors are incorporated into the calculations: the best available information on open fracture infection rates from the literature,¹ and the estimated casemix of open fracture types encountered by participating HEMS services. These estimates are necessarily imprecise, but the best possible estimates were generated based upon the literature and upon preliminary analyses of HEMS program data.
 - c. To determine the open fracture types (Gustilo and Anderson classification, see above) transported by HEMS, the investigators performed a review of transports of one participating study HEMS program (Boston MedFlight). The findings of that (unpublished) review have been used to calculate the casemix of HEMS-transported

(scene mission) patients, to enable estimation of fracture types transported, and attendant baseline risks of infection.

- d. The assessment of Boston MedFlight's casemix revealed that Type I open fractures are rarely diagnosed in the HEMS prehospital setting. This is probably due to two factors. First, the major-trauma patients transported by HEMS are relatively less likely to have the smaller-size skin disruption characterizing Type I fractures. Second, even when HEMS patients do have Type I fractures, these injuries (with their small overlying wounds) are relatively less likely to be identified in the field.
- e. The assessment of Boston MedFlight's open fracture casemix found that roughly equal proportions of Types II and III, with the exception that vascular compromise (IIIa) was found at about a third of the rate of the other types. Thus, the overall estimate of open fracture types and infection risks encountered by HEMS, for purposes of study sample size and power calculations, is as follows:
 - Type II – 30%
 - Type IIIa – 30%
 - Type IIIb – 30%
 - Type IIIc – 10%
- f. The next step in sample size calculations is to estimate infection rates associated with the open fractures transported (from scenes) by HEMS. Review of the Boston MedFlight records indicated that most (over $2/3^{\text{rds}}$) patients did in fact have risk factors noted above, to be associated with increasing fracture site infection (*e.g.* tibial involvement, smoking status, comorbidities such as diabetes). Rather than assume the overall infection risk of 31% associated with presence of 2 or more of these risk factors,²⁵ the TREAT Fx sample size and power calculations take a more conservative approach, of using the upper end of the estimated infection risks (for each open fracture type) from the 2007 review by Zalavras *et al.*¹
- g. Using the upper end of the open fracture infection risks from the Zalavras review, and weighting these estimated risks in accordance with the estimated proportions of HEMS-transported open fracture types, yields an overall estimated infection rate of 26%. Given the propensity of HEMS-transported patients to have fracture parameters (*e.g.* contamination, tibial involvement) and patient characteristics (*e.g.* smoking, systemic immunocompromise due to multisystem trauma) increasing infection risk, the 26% estimate appears reasonable.
- h. The next step in sample size calculations is the determination of the number of open fractures that must be analyzed, to detect a given relative decrease in infection risk from baseline (*i.e.* non-HEMS administration of IVAT). Calculations reveal that:
 - To enable 80% power for detection of a 25% relative reduction (from 26% to 19.5%), 1366 fracture sites must be analyzed.
 - To enable 80% power for detection of a 50% relative reduction (from 26% to 13%), 320 fracture sites must be analyzed.
- i. Many patients will have multiple open fractures, and thus the number of patients required, is less than the number of fracture sites needed for analysis.
 - An analysis of the initial 93 patients in a multi-program survey of some TREAT Fx participating programs finds that there are 115 fracture sites per

- 100 patients.
- Given the above, TREAT Fx sample size and power analyses account for this by multiplying the previously calculated n of fracture sites needed, by 85% to arrive at the estimated number of patients.
- j. The final power calculations are thus:
 - n of subjects required to detect 25% infection rate reduction: 1161
 - n of subjects required to detect 50% infection rate reduction: 272

Timeline

A. Planning phase

1) Pilot study and IRB approval

TREAT Fx study planning started in 2008, with collection of information from the pilot study used for power and sample size calculations. That information, analyzed in October 2008, will be presented in abstract form (meeting to be determined). During the pilot study, approval was obtained from the TREAT Fx “home” Institutional Review Board at Massachusetts General Hospital (Partners HealthCare IRB, reproduced in Appendix I). That IRB approval also covers data collection through the next phase of TREAT Fx (the renewal for IRB approval is scheduled for October of 2009).

2) Dissemination of study information

In November 2008, the study information and draft protocol will be disseminated. Information will be sent to HEMS programs participating in the pilot study, and also to HEMS programs already indicating interest in serving as co-investigator sites. The CCT CORE website will be used as a means to communicate about the existence of, and planning process for, the TREAT Fx study. The plan is to assemble all co-investigator sites by the end of December 2008.

B. Subject accrual/data entry phase

1) Data accrual

Data accrual starting times may vary, depending on participating programs’ resources and ability to collect data in the absence of confirmed grant support. Participating HEMS programs’ “official” data collection and study accrual are planned to commence if grant support is obtained (to support time requirements for data abstraction and entry into CCT CORE’s web interface).

No data will be able to be entered into the CCT CORE web interface, until the interface has been programmed and implemented. This will occur if and when sufficient grant support is obtained, to set up the TREAT Fx data entry module on the CCT CORE website. Data can be collected by an individual program, and kept at that program site, until such time as the web-based interface is available after appropriate grant support has enabled the requisite programming time.

In terms of the required time frame to collect subjects for the study, the sample size calculations outlined above, reveal a need for 1161 patients. Preliminary analysis of four separate programs participating in the TREAT Fx pilot study, finds that over a 4-month period these programs contributed about 2 patients per week (*i.e.* two scene responses per week, for patients

whose injuries include suspected open fractures). While this number will of course vary with program, and with time of year, an estimate of 2 patients per program per week is appropriately conservative.

Given the anticipated number 2 patients per program per week, a general estimate can be calculated as to overall study patient accrual. The following table portrays the number of annual study patients that can be expected to be accrued, given differing numbers of participating programs.

<u># Programs</u>	<u>Total study n per year</u>
3	312
5	520
7	728
9	936
10	1040
12	1248

Even though the above data are based upon estimates, it seems clear that a multicenter trial can feasibly accrue, within a reasonable time period, sufficient n to execute assess TREAT Fx clinical endpoints. If a dozen programs participate (and roughly this number of programs have already expressed interest), the study could be done in as little as a year. However, the conservative plan will be to complete the study over a two-year period. Such a time frame also accounts for the fact that there may not be completely equal split between participating programs' administration (vs. non-administration) of prehospital IVAT for open fractures. The programs that transition from not giving IVAT, to providing such therapy, can provide "program-months" to each of the study's main groups (*i.e.* HEMS Abx and Hosp Abx groups). (Another means of viewing the study's accrual requirements, is that 144 program-months will be sufficient to achieve the study n .)

2) Sources for obtaining data

The primary mechanisms for obtaining data for entry into the TREAT Fx study will be review of medical records information. Data will come from the HEMS record (*e.g.* prehospital times), the ED chart (*e.g.* times for hospital-initiated IVAT), and hospital-record information (*e.g.* operations and infection/non-union adjudication). These data can be assessed by simple review of the hospital record.

The cost data for the study will be obtained from review of administrative records of the HEMS services and of the admitting hospital. Costs assessed will be in the form of charges billed, by the HEMS service and also by the hospital. For assessment of the costs associated with the open fracture, chart reviewers will identify costs such as antibiotic therapy (for open fracture treatment) and return trips to the operating room for treatment of open fracture.

For any cases where there is uncertainty about whether to attribute particular costs to the open fracture, an abstract of the clinical information will be presented to an orthopedist participating in the study (but blinded to whether patients received prehospital IVAT), and that person will make a judgment as to whether costs were attributable to the open fracture.

3) Data entry mechanisms

Participating centers will be encouraged to enter data into the centralized TREAT Fx database using the CCT CORE website (www.cctcore.org). The CCT CORE Airway Study's mechanisms for programming the CCT CORE web-based data entry – and in fact many of the exact same fields – will be reproduced in the TREAT Fx study. (An example electronic case report form from the Airway Study is depicted in Appendix II.) This will markedly reduce the programming time and resources required for establishment of the TREAT Fx data entry interface. As was the case for the CCT CORE Airway Study, all data entry mechanisms will be encrypted, and otherwise compliant with IRB and HIPAA-type regulations.

The “up-front” work done for the CCT CORE Airway Study, was planned from that study's inception to be transportable to any follow-up CCT CORE studies. Thus, in this way, the follow-up study resource investment for information technology will be markedly reduced (nearly all of the CCT CORE funds have ended up going for IT infrastructure/programming setup). The web interface's existing fields can easily be modified, with an approach of simply retyping field names rather than programming new fields from scratch.

As was the case with the CCT CORE Airway Study, the participants will be offered assistance with data entry. This will be in the form of research assistants that are usually available to the PI. This avenue of data entry was used by some CCT CORE Airway Study, and may allow for participation by a few programs that would not otherwise be able to join TREAT Fx.

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Appendix I: IRB Approval



Partners Human Research Committee
Partners Human Research Office
116 Huntington Avenue, Suite 1002
Boston, MA 02116
Tel: (617) 424-4100
Fax: (617) 424-4199

Application: Notification of IRB Approval/Activation

Protocol #: 2008-P-001471/1; MGH

Date: 08/15/2008

To: Stephen Thomas, MD, MPH
Emergency Service
EOO Suite 3B

From: Fred Syllien
PHS Research Management
116 Huntington Ave Suite 1002

Title of Protocol: Prehospital Administration of Antibiotics in Open Fractures
Version Date: 08/01/2008
Sponsor: Internal Funding
IRB Review Type: Expedited
Minimal Risk: 45 CFR46.110 and 21 CFR56.110
Expedited Category/ies: (5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
IRB Approval Date: 08/10/2008
Approval Effective Date: 08/15/2008
IRB Expiration Date: 08/10/2009

This Project has been reviewed and approved by the MGH IRB, Assurance # FWA00003136. During the review of this Project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for securing and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Appendix II: Sample eCRF (electronic case report form) for web-based data entry from CCT CORE Airway Study

**CCT CORE Airway Project
Electronic Case Report Forms (eCRFs)**

[LOG OUT](#)

CREW ASSESSMENT OF AM DIFFICULTY AND REASONS FOR DIFFICULTY

Crew Assessments	5-point scale rating (1 easiest, 5 hardest)				
	1	2	3	4	5
ETI difficulty likelihood, before ETI/airway management was attempted	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
ETI difficulty as rated after ETI/airway management was attempted	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Airway management perceived as difficult because of inadequate muscle relaxation	<input type="radio"/> Yes		<input type="radio"/> No		
Airway management perceived as difficult because of patient anatomical (non-injury-related) factors	<input type="radio"/> Yes		<input type="radio"/> No		
Airway management perceived as difficult due to peri-airway/orofacial trauma	<input type="radio"/> Yes		<input type="radio"/> No		
Perceived airway management difficulty due to obscuration of airway by blood, vomitus, or secretions AM Diff Access	<input type="radio"/> Yes		<input type="radio"/> No		